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## RESEARCH ARTICLE

# INTERLEUKIN-17: A CARDIAC BIOMARKER IN ESTIMATION OF CARDIOPROTECTIVE EFFECTS OF TACROLIMUS IN DOXORUBICIN-INDUCED CARDIOTOXICITY: ANIMAL MODEL STUDY

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### ABSTRACT

**Background:** Doxorubicin induced cardiotoxicity includes various cardiac effects ranging from mild arrhythmias to cardiomyopathy. Coronary endothelial cells regarded as sites for the action of IL-17, via producing neutrophil chemoattractants and expressing adhesion molecules concerned in leukocyte migrations. Therefore, coronary endothelium regarded a principal consign of IL-17 role. Tacrolimus prevent mitochondrial permeability transition pore opening at the onset of reperfusion so it will limiting myocardial infarction size and cardiotoxicity.

**Aim:** The aim of present study is to evaluate the role of IL-17 in detection of cardiotoxicity and elucidate the cardioprotective effects of tacrolimus in doxorubicin-induced cardiotoxicity.

**Methods and results:** Sixty Dwale –Sprague male rats where used in this study to observe the cardioprotective effects of tacrlimus in doxorubicin induced cardiotoxicity. Doxorubicin produces significant elevation in serum MDA, LDH, Troponin and IL-17 levels as compared to the control group. While pre-treatment with tacrolimus there was a significant reduction ( $p<0.05$ ) in serum MDA, LDH, Troponin and IL-17 levels as compared to the control group.

**Conclusion:** In conclusion tacrolimus produce significant cardioprotection from doxorubicin induced cardiotoxicity with lowering IL-17 serum level.

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### INTRODUCTION

Doxorubicin induced cardiotoxicity includes various cardiac effects ranging from mild arrhythmias to cardiomyopathy via different mechanisms like free radical formation , induction of immunogenic reaction , disturbance of cardiac calcium homeostasis and changes in metabolic lipid peroxidation [Minotti *et al.*2004; Duggan and Keating,2011].

Doxorubicin lead to early onset cardiotoxicity within one year of initial therapy may be (acute, subacute and chronic) and late onset within 20-30 years after completion of doxorubicin chemotherapy [Chatterjee *et al.*2010].

Doxorubicin cardiotoxicity monitored and diagnosed via different methods like endomyocardial biopsy and imaging studies ,but these procedures are limited due to invasiveness and require cost ,so simple but not sophisticated methods are required for diagnosis and monitoring of cardiotoxicity like serum troponin ,natriuretic peptid (BNP , ANP and pro-BNP) BNP is more sensitive than ANP in cardiotoxicity ,so further need for biomarker that detect and early predict cardiac damage and cardiotoxicity[Baldeviano *et al.*2010 ] .

So, in the present study, we introduce IL-17 as biomarker for detection of doxorubicin induced cardiotoxicity.

Interleukin-17 is a fundamental mediator of neutrophil recruitment and migration during initiation the production of chemokines, like macrophage inflammatory protein-2 (MIP-2) .Also; IL-17plays a significant role in pathogenesis of viral myocarditis, dilated cardiomyopathy, cardiotoxicity and atherosclerosis[Pappu *et al.*2010 ] .

IL-17-producing CD4 called Th17 cells, IL-17 family ligands are (IL-17A to IL-17F) while IL-17 receptors are IL-17A to IL-17E have been recognized. Th17 cells as well release IL-21 and IL-22,as well, transforming growth factor (TGF) and IL-6 was intended for development of naïve T cells into Th17 cells. Furthermore,IL-1 might support Th17 detection, and IL-23 is requested for preserving Th17 cells [ Hartupee *et al.*2007 ] . Interleukin-17 protein is secreted as a disulfide-linked homodimeric glycoprotein and induces several proinflammatory cytokines and chemokines [Numasaki *et al.* 2004 ] .IL-17 also have an important function in the inflammatory process that induced by doxorubicin, it also induces inductionof the pro-inflammatory cytokines such as

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TNF- $\alpha$ , interleukin-1, and interleukin-6 [Mc Geachy and Cua, 2008].

Furthermore, IL-17 improved neutrophil penetration via advance E-selectin (EC) and ICAM-1 expression. Surprisingly, IL-17 performs a link between adaptive and innate immunity during inflammatory reaction, this give an idea in role of IL-17 in cardiotoxicity, moreover, it induced apoptosis via direct effect on cardiomyocytes and indirect effect as a mediator that organize extra mediators, as well; IL-17 had direct pro-apoptosis action to cardiac myocyte via inductions of Fas mRNA and Bcl-2 family proteins that encourage and force cardiomyocyte into apoptosis [Chang *et al.* 2008].

Neutrophils interactions required to pass the endothelium are synchronized through induction of E-selectin which is a key molecule in progressing, while ICAM-1 is a significant in adhesion so deficiency in either ICAM-1 or E-selectin lead to marked reduction in neutrophil accumulations and myocardial damage. Moreover; anti-IL-17 inhibits appearance of ICAM-1 and E-selectin thus, IL-17 has an effective effect on neutrophil recruitment and adherence, which has crucial way in doxorubicin induced cardiotoxicity [Baldeviano *et al.* 2011]. Moreover, coronary endothelial cells regarded as sites for the action of IL-17, via producing neutrophil chemoattractants and expressing adhesion molecules concerned in leukocyte migrations. So; coronary endothelium regarded a principal consist of IL-17 role. Furthermore, actions of IL-17 are reliant on the p38 MAPK pathway, so; p38 MAPK may be eventual drug target, and IL-17 could support metastasis via reduction of cancer cell adhesion. IL-17 in circulation was more in acute coronary dysfunction induced by cardiotoxic agents in comparison with patients with stable angina; also there is no interaction between blood concentration of IL-17 and other inflammatory cytokines that found to be activator of Th17 immune responses [Li *et al.* 2010]. Moreover, IL-17 was produced by coronary artery-infiltrating T cells which provoke proinflammatory reaction in cardiomyocytes [Iyoda *et al.* 2010]. Thus, IL-17 regarded as an important cytokine in induction of doxorubicin-induced cardiac damage [Venkatachalam *et al.* 2008].

Furthermore, myocardial damage also caused via doxorubicin induced neutrophils activation which release myeloperoxidase and IL-17 so; these mediators regarded as powerful indicators of cardiomyocyte injury [Barry *et al.* 2007].

Interleukin 17 stimulate p38-MAPK leading to cardiac ischemic-reperfusion injury and heart failure,  $\beta_2$ -adrenoceptor also stimulate this pathway in rat myocardium via transmembrane activation of tyrosine kinase and matrix metalloproteinase [Fatih *et al.* 2013]. Tacrolimus suppresses many of lymphokines such as interleukin-2 (IL-2) and antiapoptotic proteins, the growth factor- $\beta$  that consider as a potent inhibitor of (IL-2), thus tacrolimus will increase the expression of growth factor- $\beta$ , from (IL-2) stimulated T-cell proliferation, thus, tacrolimus inhibit synthesis and release of (IL-2) and inhibition of T-lymphocyte activation [Bernuzzi *et al.* 2009].

In cardiotoxicity induced by doxorubicin there is an induction of mitochondrial permeability transition pore which considered as critical determinant of cardiomyocyte death, and because of tacrolimus prevent mitochondrial permeability transition pore

opening at the onset of reperfusion so it will limiting myocardial infarction size and cardiotoxicity [Zhang *et al.* 2009]. Moreover, ischemic heart diseases lead to free radical production and consequently will combined with membrane phospholipids and cause lipid peroxidation. Therefore; mitochondrial dysfunction may increase ischemic injury and cardiotoxicity [Huelsenbeck *et al.* 2011], this lead to cell depletion of high-energy phosphate due to mitochondrial enzyme dysfunction and consequently mitochondrial membrane will depolarized and mitochondrial membrane transition pores will opened therefore; the mitochondrial reactive oxygen species will increase and exacerbates the oxidative stress [Jordán *et al.* 2011]. Therefore, the utilize of tacrolimus will protect the heart from oxidative stress and has protective effect on cardiomyocyte [Shen *et al.* 2009].

Therefore, the aim of present study is to evaluate the role of IL-17 in detection of cardiotoxicity and elucidate the cardioprotective effects of tacrolimus in doxorubicin induced cardiotoxicity.

### Animals and methods

This study is approved in Department of Pharmacology, College of Medicine, Al-Mustansiriya University, Baghdad-Iraq, 2014. It is permitted by the scientific Jury in Department of Pharmacology and qualified by the board of Medical College; also the ethics committee for animal experimentation approved this study. During the experiments, all animals deal with human care according to the criteria mentioned in the 'Guide for the Care and Use of Laboratory Animal' made by the Science National Academy and Published by the Health National Institute.

Sixty Ddwale -Sprague male rats were used in this study, the animals were obtained from infertility institute of AL-Nahrain Medical College. Their body weight ranged from 300 -350 gm the rats were housed in cages and kept at 25C and artificial 12 light-dark cycles they had free access to drink water and libitum, and were left for two weeks without interference for acclimatization. They had no manifestation of any illness upon examination.

After two weeks acclimatization period, the animals were randomly divided into three groups (20 animals /group)

**Group I:** received normal saline (5ml/kg), orally, daily for ten days and serve up as control.

**Group II:** received a single dose doxorubicin (15mg/kg), intraperitoneal and was sacrificed after 72 hours, which served as doxorubicin group.

**Group III:** received tacrolimus (0.1mg/kg), orally, daily for ten days, and on day eight, 6 hour after a single dose of doxorubicin (15mg/kg), intraperitoneal was given. Then blood (2.5ml) was obtained from sacrificed animal in the tenth day of treatment obtain from heart tissue, each blood sample was placed in EDTA-free tube to be centrifuged for 10 minutes at 3000 rpm. Serum was stored at (-20) until time for the assay.

### Biochemical assays

Measurement of serum interleukin 17: sandwich-Elisa method used in this Elisa kit (Interleukin 17.ELISA KIT catalog NO: E-EL-Ro566 pg/ml, Elabscience, China).

Measurement of serum cardiac Troponin I: sandwich-Elisa method used in this Elisa kit (Cardiac Troponin I ELISA KIT catalog NO: E-EL-R1253 pg./ml, Elabscience, China)

Measurement of serum malondialdehyde (MDA): competitive-Elisa method used in the Elisa kit ((MDA) ELISA KIT catalog NO:E-EL-0060 ng/ml, Elabscience, China)

Measurement of serum lactate dehydrogenase (LDH): absorbance due to NADH to NAD directproportional to LDHactivity in the specimen is measured at 340 nm.( Lactate Dehydrogenase (LDH)pmol/ml, BIOLABO, France)

**Histopathological Estimation**

The heart after obtained were immediately emerged in iced normal saline to prevent heart ischemic injury that may happen from further beating then, the animal heart placed in formaldehyde (10%) ,to harden the tissue and to prevent tissue structural changes due to autolysis via tissue enzymes.[]

Fixation of animals heart in formaldehyde (10%) then tissue dissection and cross sectional cut were done to obtain the ventricles .The sections obtained were stained with Hematoxylin and Eosin (H&E) and visualized under light microscope to study the light microscopic architecture of the myocardium. The pathologist performing the histological grade evaluation was blinded to treatment allocation. The following light microscopic features were used to assess the histopathological damage[ Jian *et al.* 2013 ] .

**Statistical analysis** results were expressing as mean±SE (standard error). student T-test and ANOVA test were used to examine the degree of significance ,where P value<0.05 was considered significant.

**RESULTS**

**Biomarkers results**

Doxorubicin produces significant elevation in serum MDA,LDH, Troponin and IL-17 levels as compared to the control group.

While pre-treatment with tacrolimus there was a significant reduction (p<0.05) in serum MDA, LDH, Troponin and IL-17 levels as compared to the control group table (1).

Serum MDA significantly elevated in doxorubicin treated group as to control and tacrolimus figure (1)

Doxorubicin drug produces significant elevation (p<0.05) in serum Troponin I level in doxorubicin group as compared to the normal control group. While Pre-treatment with tacrolimus produced significant reduction (p<0.05) in serum Troponin I level as compared to the doxorubicin group figure(2).

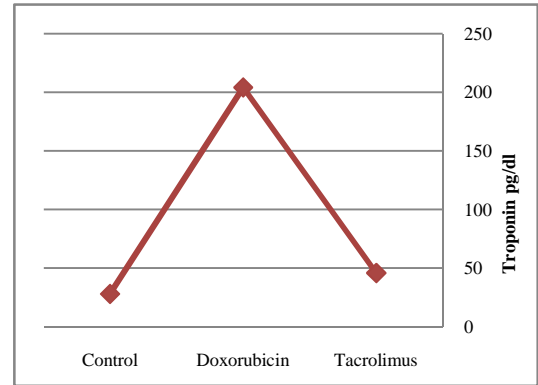


Figure 2 reduction in the level of troponin I in tacrolimus treated group in comparison with doxorubicin group.

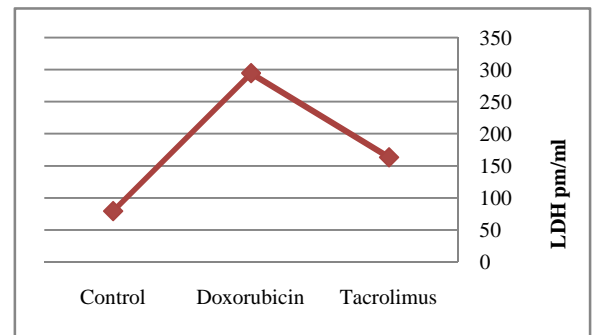


Figure 3 reduction in the level of LDH in tacrolimus treated group in comparison with doxorubicin group.

**Table 1** effect of doxorubicin alone and with tacrolimus pretreatment on cardiac biomarkers.

Cardiac biomarkers	Control (n=10)	Doxorubicin (n=10)	Tacrolimus(n=10)
Serum MDA ng/ml	30.066±1.8	290.06±1.85"	121.55±1.29*
Serum Troponin-Ipg/ml	28.07±1.5	204.12±1.08"	45.92±0.55 *
Serum LDHpmol/ml	79.2±1.99	294.14±0.93"	163.04±3.09 *
Serum IL-17 g/ml	56.01±1.58	246.02±2.68"	168.3±1.27 *

Data presented as Mean ±SE \*p<0.01,"p<0.001 on comparison with control.

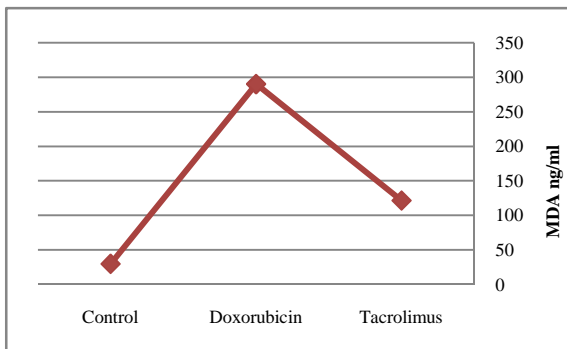


Figure 1 MDA levels in tacrolimus, control and doxorubicin treated groups.

Also, doxorubicin produced significant elevation (p<0.05) in serum LDH level in doxorubicin treated group as compared to the normal control group. While pre-treatment with tacrolimus created significant reduction (p<0.05) in serum LDH levels compared to the doxorubicin group figure (3).

Regarding IL-17 level in cardiotoxicity ,doxorubicin drug lead to significant elevation (p<0.05) in serum (IL-17) level in doxorubicin group as compared to the normal control group while, pre-treatment with tacrolimus produced significant reduction (p<0.05) in serum (IL-17) level as compared to the doxorubicin group figure(4).

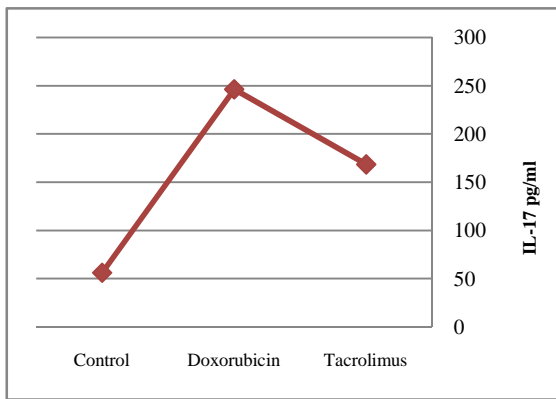


Figure 4 reduction in the level of IL-17 in tacrolimus treated group in comparison with doxorubicin group.

Moreover; there is a significant correlation among elevation in cardiac biomarkers induced via doxorubicin cardio toxicity. IL-17 significantly correlated with troponin I in doxorubicin induced cardiotoxicity figure (5).

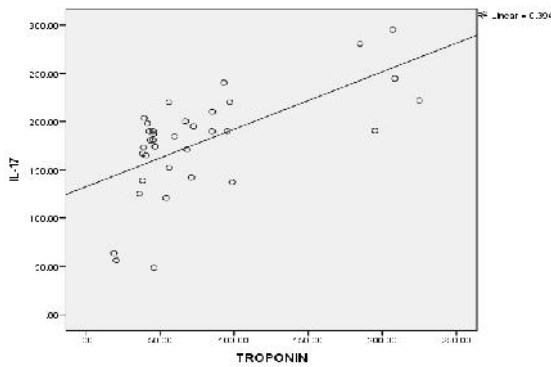


Figure 5 correlations between IL-17 and serum troponin I.

Moreover; there is significant correlation between IL-17 and LDH and MDA in serum of doxorubicin induced cardiotoxicity figure (6,7).

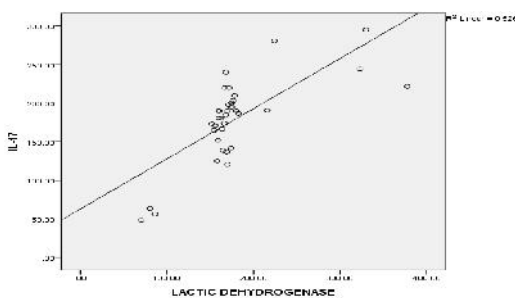


Figure 6 correlation between IL-17 and serum LDH.

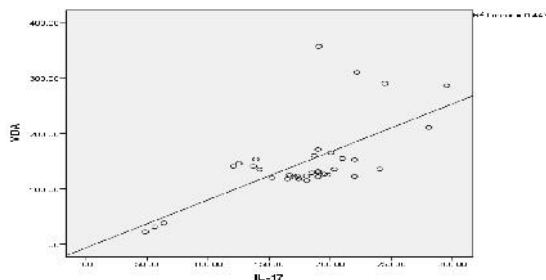
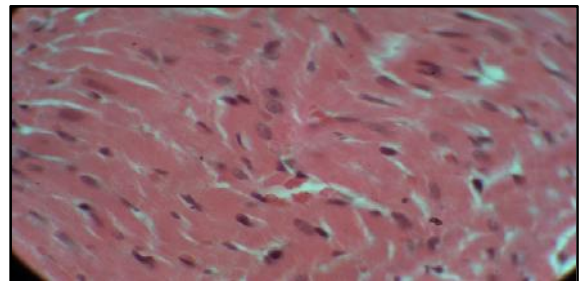


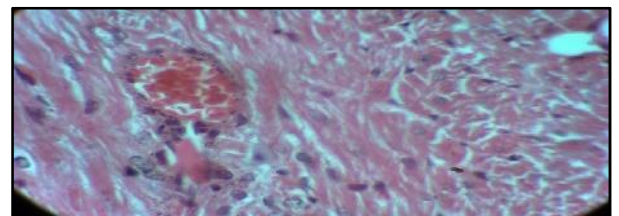
Figure 7 correlation between IL-17 and serum MDA.

### Histopathological results

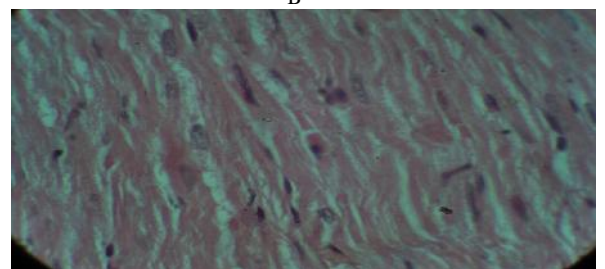
Control group showed a normal cardiac tissue with multiple peripheral nuclei and branching striated muscle fibers, while in doxorubicin treated group there are congested blood vessels with extravasations, fragmentation of myocardial muscle fibers and edema. Tacrolimus produced significant amelioration of nuclei and striated muscle fibers and disappearance of congestion and extravasations Image(1).



A



B



C

Image(1):light microscope of heart sections:(A) control group-normal cardiac morphology , Sections of normal myocardial tissue control group shows multiple peripheral nuclei with branching striated muscle fibers, 100X , (B) group treated with doxorubicin - section of cardiac tissue with treatment of doxorubicin shows congested blood vessels, appearance of multiple vacuoles and segmental loss of normal tissue architecture , 100X,(C) group pretreated with tacrolimus shows-less vacuolization of cardiomyocytes plus preserved cardiac structure(H&E  $\times 40$ )

### DISCUSSION

In doxorubicin induced cardiotoxicity there is damage of sarcolemmal membrane leading to intracellular  $Ca^{2+}$  overload that induce opening of MPTP ,also ;this toxicity lead to complement activation which lead to direct cardiac damage or through activation of releasing of inflammatory or proinflammatory cytokines like interleukin -17 ,platelet activating factor(PAF) and histamine also, this lead to induction of superoxide production and oxidative stress damage that induce alterations in membrane phospholipids and protein ,all these lead to inflammatory micro-vascular dysfunction , and then cardiac damage [Kalyanaraman *et al.*2002 ].



So, in the present study there are significant elevations in cardiac biomarkers which reflect doxorubicin cardiotoxicity that raising serum level of MDA, LDH, and IL-17 significantly in comparison with control.

Pretreatment with tacrolimus protect the heart from toxic effects of doxorubicin thus, tacrolimus significantly reduces the cardiac biomarker, which reveal cardioprotection effects from doxorubicin induced cardiotoxicity.

Tacrolimus produced its action through a high affinity to cyclophilin-A, while its cardioprotective effect related to inhibition of cyclophilin-D [Schreiber, 1991]. Cyclophilin-D is a key constituent of mitochondrial permeability transition pore (MPTP), in chemotherapy induced cardiotoxicity and cardiac reperfusion-ischemic injury there is induction of MPTP [Yongzhi *et al.*2009], therefore; tacrolimus reduces the myocardial infarction size in mice but not in mice deficient cyclophilin-D [Krishnadasan *et al.*2002].

Numerous human studies showed that tarolimusreduced cardiac infarction size after reperfusion in percutaneous coronary intervention for ST-elevation myocardial infarction ,also; post resuscitation administration of tacrolimus lead to bell shaped cardiac conservation in animal model study[Nishinaka *et al.*1993 ], this improvement in cardiac function is more probable related to preservation of cardiomyocytes .

Tacrolimus at dose of 2.5mg/kg lessen the cardiac damage up to 40% as compared to control , this evident via low level of troponin-I and cardiac creatin-phosphokinase ,thus ;tacrolimus dose ranged at 1-5 mg/kg produced significant cardioprotection [ Nakata *et al.*2000 ] .

Calcineurin pathway was linked to cardiac hypertrophy ,thus; tacrolimus which is calcineurin pathway inhibitor produced significant cardioprotection ,angiogenesis ,inhibit cardiac hypertrophy and improve vascular endothelial function via activation of vascular endothelial growth factor (VEGF)inhibit oxidative stress ,induce NO production ,moreover ,tacrolimus inhibit fetal gen expression that linked to cardiac remodeling and hypertrophy[Crabtree and Olson,2002 ] .

Tacrolimus inhibit myocardial inflammation through inhibition of CD26 circulation and adherence to cardiomyocete, also it decrease IL-17 production and its deleterious effects on cardiomyocytes [Wilkins *et al.* 2004] .

Tacrolimus have a special effects on CD4, via inhibition of IL-15 dependent production of IL-17 in CD4 which is dose-time dependent, throughout activation of molecular signaling including PI3K/Akt and NF-kB pathway, therefore; inhibitors for either PI3K/Akt or NF-kB inhibit IL-17 production, thus tacrolimus inhibit these signaling leading to reduction in IL-17, consequently; tacrolimus produced cardioprotective effect from damaging effect of IL-17 [Fábrega *et al.*2009].

Moreover; diminish in IL-17 in the existence of tacrolimus therapy possibly, via downregulation of IL-6,it is probable that tacrolimus may normalizes proinflammatory cytokines and block in vitro production of IL-17 and IFN [Afzali *et al.*2010 ] . Additionally; tacrolimus inhibit calcineurin substrate called nuclear factor of activated T-cell (NFAT) which responsible for IL-17 gene expression and production of other cytokines, also the NFAT activate MAPK leading to inflammatory activations [Shioi *et al.*2002 ] .

Furthermore; myocardial damage also caused via doxorubicin induced neutrophils activation which release myeloperoxidase and IL-17 so; these mediators regarded as powerful indicators of cardiomyocyt injury .Therefore; reduction of IL-17 via pretreatment with tacrolimus indicate a protective role in acute coronary syndrome[Madhur *et al.*2010 ] .

Regarding histopathological changes, in the doxorubicin lead to congested blood vessels with fragmentation of muscle fibers, edema and extravasations in cardiac tissues section [Lipshultz *et al.*2005].

While; in the group pre-treated with tacrolimus shows no congestion in blood vessels, with less fragmentation of myocardial muscle fiber, restoration of nuclei number, less edema and vacuolation. Thus; tacrolimus produced significant tissue protection though anti-inflammatory, antioxidant and others mechanisms that afford cell and cell matrix guard from doxorubicin induced cardiotoxicity [Meenakshi *et al.*2014 ] .

## CONCLUSION

Tacrolimus produce significant cardioprotection from doxorubicin-induced cardiotoxicity with lowering IL-17 serum level.

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## Conflict of interest

The authors declare no conflict of interest.

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